

Ottawa Hull K1A 0C9

(21) (A1) 2,136,288  
(22) 1994/11/21  
(43) 1995/05/24

(51) Int.Cl. <sup>5</sup> C07D 487/04; C07D 519/00; A61K 31/495; A61K 31/535

(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Imidazopyridazines

(72) Dorsch, Dieter - Germany (Federal Republic of) ;  
Mederski, Werner - Germany (Federal Republic of) ;  
Osswald, Mathias - Germany (Federal Republic of) ;  
Schelling, Pierre - Germany (Federal Republic of) ;  
Beier, Norbert - Germany (Federal Republic of) ;  
Lues, Ingeborg - Germany (Federal Republic of) ;  
Minck, Klaus-Otto - Germany (Federal Republic of) ;

(71) Merck Patent Gesellschaft mit beschränkter Haftung -  
Germany (Federal Republic of) ;

(30) (DE) P 43 39 868.5 1993/11/23

(57) 8 Claims

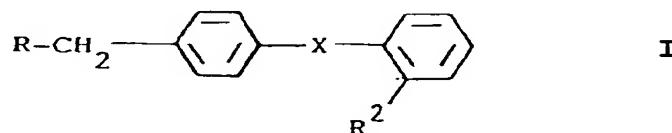
Notice: This application is as filed and may therefore contain an incomplete specification.



2136288

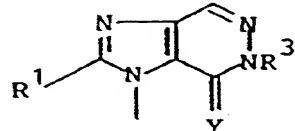
**Abstract of the Disclosure**

**Novel imidazopyridazine derivatives of formula I**



wherein

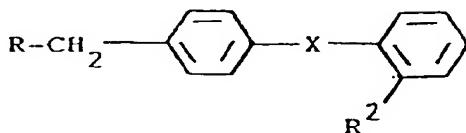
R is



and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X and Y are as defined in Patent Claim 1, and their salts, exhibit antagonistic properties towards angiotensin II and can be used for the treatment of hypertension, aldosteronism, cardiac insufficiency and increased intraocular pressure, and of disorders of the central nervous system.

## Patent Claims

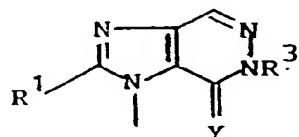
1. Imidazopyridazine derivatives of formula I:



I

wherein

5 R is



R<sup>1</sup> is A, alkenyl or alkynyl each having up to 6 C atoms, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl-C<sub>k</sub>H<sub>2k</sub>- or C<sub>1</sub>-C<sub>6</sub>-alkyl, wherein a CH<sub>2</sub> group is replaced by O or S,

10 R<sup>2</sup> is H, COOH, COOA, CN, NO<sub>2</sub>, NH<sub>2</sub>, NH-COR<sup>4</sup>, NH-SO<sub>2</sub>R<sup>4</sup> or 1H-tetrazol-5-yl,

15 R<sup>3</sup> is a C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl group which is mono- to tetrasubstituted by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, CN, COOH, COOA, Ar, Het<sup>1</sup>, Het<sup>2</sup>, -CO-R<sup>5</sup>, -CO-Ar, -CO-Het<sup>2</sup>, -CO-NR<sup>6</sup>R<sup>7</sup>, -CO-R<sup>8</sup>, -C(=NR<sup>9</sup>)-A, -C(=NR<sup>9</sup>)-Het<sup>2</sup>, NO<sub>2</sub>, NR<sup>6</sup>R<sup>7</sup>, -NR<sup>11</sup>-COR<sup>5</sup>, -NR<sup>11</sup>-COAr, -NR<sup>11</sup>-COOA, -NR<sup>11</sup>-SO<sub>2</sub>R<sup>5</sup>, -NR<sup>11</sup>-SO<sub>2</sub>Ar, OR<sup>10</sup>, -S(O)<sub>m</sub>-A, -S-(O)<sub>m</sub>-Ar, -SO<sub>2</sub>-NH-Het<sup>2</sup>, -SO<sub>2</sub>-OR<sup>11</sup>, Hal and/or 1H-tetrazol-5-yl and in which a CH<sub>2</sub> group can also be replaced by an O or S atom; or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl,

20 R<sup>4</sup> and R<sup>5</sup> are each C<sub>1</sub>-C<sub>5</sub>-alkyl, in which one or more H atoms can also be replaced by F,

R<sup>6</sup> and R<sup>7</sup> are each H, A, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl, Ar, ArC<sub>n</sub>H<sub>2n</sub>- or Het<sup>2</sup>,

25 R<sup>6</sup> is also -CH<sub>2</sub>COOA, -SO<sub>2</sub>-A or -SO<sub>2</sub>-Ar,

R<sup>6</sup> and R<sup>7</sup> together are also an alkylene chain having 2-5 C atoms, which can be monosubstituted or polysubstituted by carbonyl oxygen, Ar, Het<sup>2</sup>, -CO-Ar, -COOA,

-CO-N(A)<sub>2</sub>, -CH<sub>2</sub>OH, -SO<sub>2</sub>-Ar and/or -NH-CO-A and/or interrupted by O or by -NR<sup>12</sup>-,

5      R<sup>8</sup>    is -NH-CHR<sup>11</sup>-COOH, -NH-CHR<sup>11</sup>-OOA, -CH<sub>2</sub>S(O)<sub>m</sub>-Ar,  
        -CH<sub>2</sub>C-COOA, -C<sub>n</sub>H<sub>2n</sub>-NO<sub>2</sub>, -C<sub>n</sub>H<sub>2n</sub>-NR<sup>6</sup>R<sup>7</sup> or -C<sub>n</sub>H<sub>2n</sub>-NH-COOA,

10     R<sup>9</sup>    is H, OH, CN, R<sup>13</sup>, OR<sup>13</sup> or OAr,  
        R<sup>10</sup>    is H, C<sub>1</sub>-C<sub>10</sub>-alkyl which can be substituted by Ar, Het<sup>2</sup>, COA or COAr, or is Ar, COA, COAr or CONR<sup>6</sup>R<sup>7</sup>,  
        R<sup>11</sup>    is H or A,  
        R<sup>12</sup>    is H, A, Ar, COOA, Het<sup>2</sup> or SO<sub>2</sub>Ar,  
        R<sup>13</sup>    is A, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl,  
        X        is absent or is -NH-CO-, -CO-NH-, -O-CH(COOH)-, -NH-CH(COOH)-, -NA-CH(COOH)-, -CH=C(COOH)-, -CH=C(CN)- or -CH=C(1H-tetrazol-5-yl)-,

15     Y        is O or S,  
        A        is C<sub>1</sub>-C<sub>6</sub>-alkyl,  
        Ar        is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R<sup>5</sup>, OR<sup>5</sup>, COOH, COOA, CN, NO<sub>2</sub>, NH<sub>2</sub>, NHA, N(A)<sub>2</sub>, NR<sup>11</sup>-COR<sup>5</sup>, NR<sup>11</sup>-COAr<sup>1</sup>, NR<sup>11</sup>-SO<sub>2</sub>R<sup>5</sup>, NR<sup>11</sup>-SO<sub>2</sub>Ar<sup>1</sup>, Hal or 1H-tetrazol-5-yl,  
        20    Ar<sup>1</sup>    is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R<sup>5</sup>, OR<sup>5</sup>, COOA or Hal,  
        Het<sup>1</sup>    is a five- or six-membered saturated heterocyclic radical having 1 to 3 N, O and/or S atoms, which can be monosubstituted by carbonyl oxygen or =NR<sup>9</sup> and/or whose ring N atom(s) can in each case be substituted by A or Ar,  
        25    Het<sup>2</sup>    is a five- or six-membered heteroaromatic radical having 1 to 3 N, O and/or S atoms, which can also be fused with a benzene or pyridine ring and/or mono-substituted or disubstituted by A,  
        Hal      is F, Cl, Br or I,  
        k        is 0, 1, 2, 3 or 4  
        30    m        is 0, 1 or 2 and  
        n        is 1, 2, 3, 4, 5 or 6,  
        and their salts.

2.    a) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-benzyl-7-oxo-1H-imidazo[4,5-

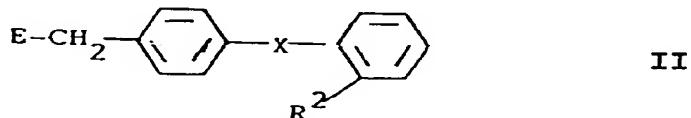
d] pyridazine and its potassium salt;

b) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6- $\alpha$ -isopropoxycarbonylbenzyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt;

c) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-N,N-dimethylcarbamoylmethyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt.

10 3. Process for the preparation of imidazopyridazines of formula I according to Claim 1, and their salts, characterized in that

(a) a compound of formula II:



15 wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and R<sup>2</sup> is as defined in Claim 1,  
is reacted with a compound of formula III:

20

H-R

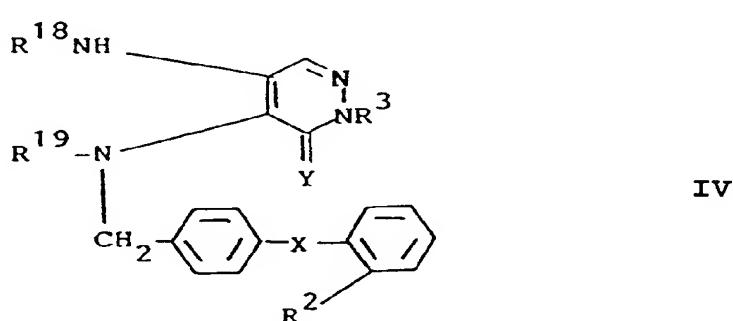
III

wherein

R is as defined in Claim 1,  
or

(b) a compound of formula IV:

25



wherein

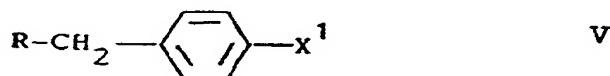
$R^{14}$  is  $R^1\text{-CO}$  or H,

$R^{15}$  is H (if  $R^{14}$  is  $R^1\text{-CO}$ ) or  $R^1\text{-CO}$  (if  $R^{14}$  is H), and  
 $R^1$ ,  $R^2$ ,  $R^3$ , X and Y are as defined in Claim 1,

5 is treated with a cyclizing agent,

or

(c) to prepare a compound of formula I wherein X is  $\text{-NH-CO-}$  or  $\text{-CO-NH-}$ , a compound of formula V:



10 wherein

$X^1$  is  $\text{NH}_2$  or  $\text{COOH}$ , and

R is as defined in Claim 1,

or a reactive derivative of this compound, is reacted with a compound of formula VI:

15



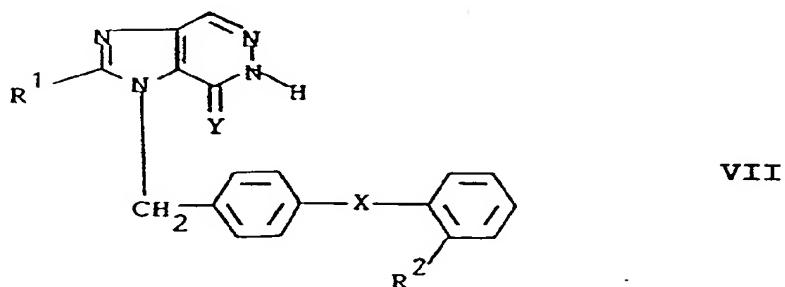
wherein

$X^2$  is  $\text{COOH}$  (if  $X^1$  is  $\text{NH}_2$ ) or  $\text{NH}_2$  (if  $X^1$  is  $\text{COOH}$ ), and  
 $R^2$  is as defined in Claim 1,

or with a reactive derivative of this compound,

20 or

(d) a compound of formula VII:



wherein

$R^1$ ,  $R^2$ , X and Y are as defined in Claim 1,  
is reacted with a compound of formula VIII:

E- $R^3$ 

VIII

wherein

5       $R^3$  and E are as defined above,  
or a reactive derivative of such a compound,  
or  
(e) to prepare a compound of the formula I which contains  
10     a  $-C(=NR^9)-$  group, a corresponding carbonyl compound is  
treated with a compound of the formula  $H_2N-R^9$ , wherein  $R^9$   
is as defined in Claim 1, or  
(f) a compound of formula I is freed from one of its  
functional derivatives by treatment with a solvolysing or  
hydrogenolysing agent,  
15     and/or in that one or more radicals R and/or  $R^2$  in a  
compound of formula I are converted to one or more  
different radicals R and/or  $R^2$ , and/or a base or acid of  
formula I is converted to one of its salts.

4.      Process for the preparation of pharmaceutical  
20     formulations, characterized in that a compound of formula  
I according to Claim 1, and/or one of its physiologically  
acceptable salts, are incorporated into a suitable dosage  
form together with at least one solid, liquid or semi-  
liquid excipient or adjunct.

25     5.      Pharmaceutical formulation, characterized in that  
it contains at least one compound of formula I according  
to Claim 1, and/or one of its physiologically acceptable  
salts.

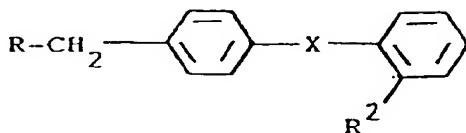
30     6.      Compound of formula I according to Claim 1, and  
its physiologically acceptable salts, for the control of  
diseases.

7.      Use of compounds of formula I according to Claim  
1, and/or their physiologically acceptable salts, for the  
preparation of a drug.

35     8.      Use of compounds of formula I according to Claim  
1, and/or their physiologically acceptable salts, in the  
control of diseases.

## Patent Claims

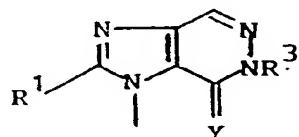
1. Imidazopyridazine derivatives of formula I:



I

wherein

5 R is



R<sup>1</sup> is A, alkenyl or alkynyl each having up to 6 C atoms, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl-C<sub>k</sub>H<sub>2k</sub>- or C<sub>1</sub>-C<sub>6</sub>-alkyl, wherein a CH<sub>2</sub> group is replaced by O or S,

10 R<sup>2</sup> is H, COOH, COOA, CN, NO<sub>2</sub>, NH<sub>2</sub>, NH-COR<sup>4</sup>, NH-SO<sub>2</sub>R<sup>4</sup> or 1H-tetrazol-5-yl,

15 R<sup>3</sup> is a C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl group which is mono- to tetrasubstituted by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, CN, COOH, COOA, Ar, Het<sup>1</sup>, Het<sup>2</sup>, -CO-R<sup>5</sup>, -CO-Ar, -CO-Het<sup>2</sup>, -CO-NR<sup>6</sup>R<sup>7</sup>, -CO-R<sup>8</sup>, -C(=NR<sup>9</sup>)-A, -C(=NR<sup>9</sup>)-Het<sup>2</sup>, NO<sub>2</sub>, NR<sup>6</sup>R<sup>7</sup>, -NR<sup>11</sup>-COR<sup>5</sup>, -NR<sup>11</sup>-COAr, -NR<sup>11</sup>-COOA, -NR<sup>11</sup>-SO<sub>2</sub>R<sup>5</sup>, -NR<sup>11</sup>-SO<sub>2</sub>Ar, OR<sup>10</sup>, -S(O)<sub>m</sub>-A, -S-(O)<sub>m</sub>-Ar, -SO<sub>2</sub>-NH-Het<sup>2</sup>, -SO<sub>2</sub>-OR<sup>11</sup>, Hal and/or 1H-tetrazol-5-yl and in which a CH<sub>2</sub> group can also be replaced by an O or S atom; or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl,

20 R<sup>4</sup> and R<sup>5</sup> are each C<sub>1</sub>-C<sub>5</sub>-alkyl, in which one or more H atoms can also be replaced by F,

R<sup>6</sup> and R<sup>7</sup> are each H, A, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl, Ar, ArC<sub>n</sub>H<sub>2n</sub>- or Het<sup>2</sup>,

25 R<sup>6</sup> is also -CH<sub>2</sub>COOA, -SO<sub>2</sub>-A or -SO<sub>2</sub>-Ar,

R<sup>6</sup> and R<sup>7</sup> together are also an alkylene chain having 2-5 C atoms, which can be monosubstituted or polysubstituted by carbonyl oxygen, Ar, Het<sup>2</sup>, -CO-Ar, -COOA,

$\text{-CO-N(A)}_2$ ,  $\text{-CH}_2\text{OH}$ ,  $\text{-SO}_2\text{-Ar}$  and/or  $\text{-NH-CO-A}$  and/or interrupted by O or by  $\text{-NR}^{12}-$ ,  
 R<sup>8</sup> is  $\text{-NH-CHR}^{11}\text{-COOH}$ ,  $\text{-NH-CHR}^{11}\text{-OOA}$ ,  $\text{-CH}_2\text{S(O)}_m\text{-Ar}$ ,  
 $\text{-CH}_2\text{C-COOA}$ ,  $\text{-C}_n\text{H}_{2n}\text{-NO}_2$ ,  $\text{-C}_n\text{H}_{2n}\text{-NR}^6\text{R}^7$  or  $\text{-C}_n\text{H}_{2n}\text{-NH-COOA}$ ,  
 5 R<sup>9</sup> is H, OH, CN, R<sup>13</sup>, OR<sup>13</sup> or OAr,  
 R<sup>10</sup> is H, C<sub>1</sub>-C<sub>10</sub>-alkyl which can be substituted by Ar, Het<sup>2</sup>, COA or COAr, or is Ar, COA, COAr or CONR<sup>6</sup>R<sup>7</sup>,  
 R<sup>11</sup> is H or A,  
 10 R<sup>12</sup> is H, A, Ar, COOA, Het<sup>2</sup> or SO<sub>2</sub>Ar,  
 R<sup>13</sup> is A, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl,  
 X is absent or is  $\text{-NH-CO-}$ ,  $\text{-CO-NH-}$ ,  $\text{-O-CH(COOH)-}$ ,  $\text{-NH-CH(COOH)-}$ ,  $\text{-NA-CH(COOH)-}$ ,  $\text{-CH=C(COOH)-}$ ,  $\text{-CH=C(CN)-}$  or  $\text{-CH=C(1H-tetrazol-5-yl)-}$ ,  
 15 Y is O or S,  
 A is C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 Ar is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R<sup>5</sup>, OR<sup>5</sup>, COOH, COOA, CN, NO<sub>2</sub>, NH<sub>2</sub>, NHA, N(A)<sub>2</sub>, NR<sup>11</sup>-COR<sup>5</sup>, NR<sup>11</sup>-COAr<sup>1</sup>, NR<sup>11</sup>-SO<sub>2</sub>R<sup>5</sup>, NR<sup>11</sup>-SO<sub>2</sub>Ar<sup>1</sup>, Hal or 1H-tetrazol-5-yl,  
 20 Ar<sup>1</sup> is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R<sup>5</sup>, OR<sup>5</sup>, COOA or Hal,  
 Het<sup>1</sup> is a five- or six-membered saturated heterocyclic radical having 1 to 3 N, O and/or S atoms, which can be monosubstituted by carbonyl oxygen or =NR<sup>9</sup> and/or whose ring N atom(s) can in each case be substituted by A or Ar,  
 25 Het<sup>2</sup> is a five- or six-membered heteroaromatic radical having 1 to 3 N, O and/or S atoms, which can also be fused with a benzene or pyridine ring and/or mono-substituted or disubstituted by A,  
 Hal is F, Cl, Br or I,  
 k is 0, 1, 2, 3 or 4  
 30 m is 0, 1 or 2 and  
 n is 1, 2, 3, 4, 5 or 6,  
 and their salts.  
 35 2. a) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-benzyl-7-oxo-1H-imidazo[4,5-

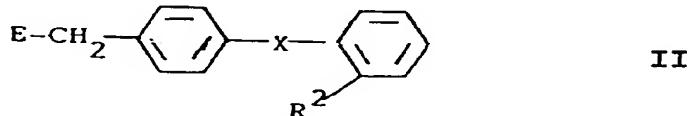
d] pyridazine and its potassium salt;

b) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6- $\alpha$ -isopropoxycarbonylbenzyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt;

c) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-N,N-dimethylcarbamoylmethyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt.

10 3. Process for the preparation of imidazopyridazines of formula I according to Claim 1, and their salts, characterized in that

(a) a compound of formula II:



15 wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and R<sup>2</sup> is as defined in Claim 1,  
is reacted with a compound of formula III:

20

H-R

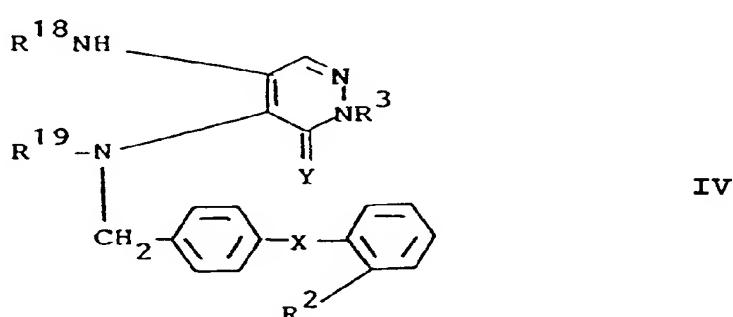
III

wherein

R is as defined in Claim 1,  
or

(b) a compound of formula IV:

25



wherein

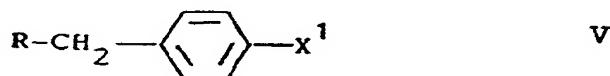
$R^{14}$  is  $R^1\text{-CO}$  or H,

$R^{15}$  is H (if  $R^{14}$  is  $R^1\text{-CO}$ ) or  $R^1\text{-CO}$  (if  $R^{14}$  is H), and  
 $R^1$ ,  $R^2$ ,  $R^3$ , X and Y are as defined in Claim 1,

5 is treated with a cyclizing agent,

or

(c) to prepare a compound of formula I wherein X is  $\text{-NH-CO-}$  or  $\text{-CO-NH-}$ , a compound of formula V:



10 wherein

$X^1$  is  $\text{NH}_2$  or  $\text{COOH}$ , and

R is as defined in Claim 1,

or a reactive derivative of this compound, is reacted with a compound of formula VI:

15



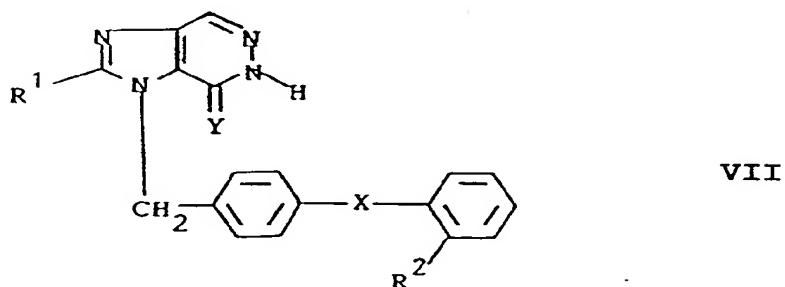
wherein

$X^2$  is  $\text{COOH}$  (if  $X^1$  is  $\text{NH}_2$ ) or  $\text{NH}_2$  (if  $X^1$  is  $\text{COOH}$ ), and  
 $R^2$  is as defined in Claim 1,

or with a reactive derivative of this compound,

20 or

(d) a compound of formula VII:



wherein

$R^1$ ,  $R^2$ , X and Y are as defined in Claim 1,  
is reacted with a compound of formula VIII:

E- $R^3$ 

VIII

wherein

5       $R^3$  and E are as defined above,  
or a reactive derivative of such a compound,  
or  
(e) to prepare a compound of the formula I which contains  
10     a  $-C(=NR^9)-$  group, a corresponding carbonyl compound is  
treated with a compound of the formula  $H_2N-R^9$ , wherein  $R^9$   
is as defined in Claim 1, or  
(f) a compound of formula I is freed from one of its  
functional derivatives by treatment with a solvolysing or  
hydrogenolysing agent,  
15     and/or in that one or more radicals R and/or  $R^2$  in a  
compound of formula I are converted to one or more  
different radicals R and/or  $R^2$ , and/or a base or acid of  
formula I is converted to one of its salts.

4.      Process for the preparation of pharmaceutical  
20     formulations, characterized in that a compound of formula  
I according to Claim 1, and/or one of its physiologically  
acceptable salts, are incorporated into a suitable dosage  
form together with at least one solid, liquid or semi-  
liquid excipient or adjunct.

25     5.      Pharmaceutical formulation, characterized in that  
it contains at least one compound of formula I according  
to Claim 1, and/or one of its physiologically acceptable  
salts.

30     6.      Compound of formula I according to Claim 1, and  
its physiologically acceptable salts, for the control of  
diseases.

7.      Use of compounds of formula I according to Claim  
1, and/or their physiologically acceptable salts, for the  
preparation of a drug.

35     8.      Use of compounds of formula I according to Claim  
1, and/or their physiologically acceptable salts, in the  
control of diseases.